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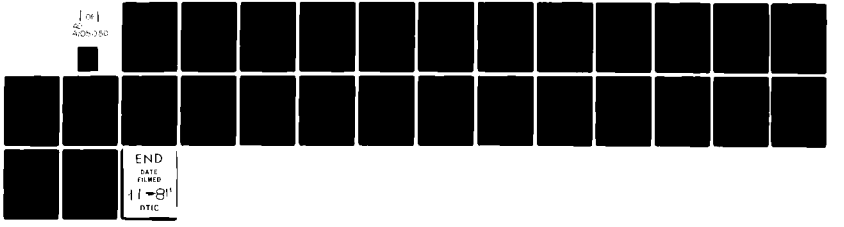

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# 24-HOUR MEAN PLASMA HORMONE LEVELS IN MEN WITH CORONARY HEART DISEASE

by

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Plasma concentrations of 14 hormones or hormone metabolites and urinary excretion of 15 hormones or hormone metabolites were studied in four rigorously selected groups: 13 men who had recovered well from prior myocardial infarction (at least 6 months earlier), 35 clinically normal men, 25 men with severe coronary artery disease diagnosed by coronary arteriograms but no history or signs of myocardial infarction, and 44 men with normal coronary arteriograms. Aside from a minor finding that a

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subset of the post-infarction patients (3 out of 12) showed subnormal plasma T3 levels (? the non-specific low-T3 syndrome), there were four major findings: post-infarction patients had significantly higher 24-hour mean plasma concentrations of estrone (80 vs 49 pg/ml, $P < 0.0001$), dehydroisoandrosterone (444 vs 298 ng/dl, $P < 0.025$), and dehydroisoandrosterone sulfate (112 vs 72 μg/dl, $P = 0.05$) than clinically normal men, while men with positive coronary arteriograms but no infarction had the same levels as men with negative arteriograms; men with positive arteriograms but no infarction had significantly lower urinary excretion of androsterone glucuronide (2.6 vs 3.2 mg/g creatinine, $P < 0.05$) than men with negative arteriograms, while post-infarction patients excreted normal amounts of this steroid. In the case of all three differing plasma steroids, nearly all the post-infarction patients had values at or below the upper 95% confidence limit of the normal range; the significant elevation of the post-infarction patients' mean value was due in each case to clustering of the patients' values in the upper half of the normal range. Similarly, the extremes of the range of androsterone glucuronide excretion were the same in men with positive or negative arteriograms; the significant difference between the mean values was due to clustering of the positive arteriogram subjects' values in the lower half of the range shown by negative arteriogram subjects.

To account for these findings, we have formulated a "selection hypothesis," i.e. that the members of the post-infarction group we studied are not a random sample of the "pre-infarction" (i.e. positive arteriogram) group, but a subset of that group who had higher than average levels of the four plasma and urinary steroids before the infarction. Such a selection process might operate in either of two ways: the higher pre-infarction levels might favor the occurrence of an infarction, or they might favor survival from an infarction once one had occurred. Experimental and epidemiological evidence favors the latter possibility.

Comprehensive list of research objectives

The objectives of this study were:

(1) to compare the 24-hour mean plasma concentrations of 14 hormones or hormone metabolites in clinically normal men and men who have had one or more myocardial infarctions

(2) to compare the same parameters in m[illegible] with negative coronary arteriograms and men with positive arteriograms but no history or evidence of myocardial infarction

(3) to compare the urinary excretion of 15 hormones or hormone metabolites in men with positive and negative arteriograms.

The purpose of these studies was to determine whether hormonal abnormalities were present in coronary artery disease, with or without myocardial infarction, and to distinguish abnormalities associated with coronary artery disease per se from those that appear only after myocardial infarction.

Status of the research

The studies have been completed. A manuscript describing the results (attached) has been submitted to Arteriosclerosis.

List of Publications

1. I gave a presentation on April 21, 1979 at Ramapo College of New Jersey, in Mahway, N.J., as part of a symposium entitled "The Sciences at the Forefront of Cardiovascular Research". The title of my presentation was "Plasma Hormone Concentrations in Coronary Disease." The proceedings of this conference will be published in 1981.

2. I gave a presentation on June 3, 1980, at Searles Castle, Great Barrington, Massachusetts, as part of a symposium sponsored by the NHLBI on the topic "The Influence of Female Sex Hormones on Vascular Disease and Thrombosis." The title of my presentation was "Plasma and Urinary Hormone Levels in Men with Coronary Artery Disease." The proceedings of this conference will be published in 1981.

3. In 1980, I submitted an essay entitled "Plasma and Urinary Hormone Levels in Men with Coronary Artery Disease" for the annual AMSUS competition for the Sir Henry Wellcome Medal. I was not selected for the prize but a portion of the manuscript is to be published in Military Medicine in 1981 (manuscript attached).

4. A manuscript (attached) entitled "Plasma and Urinary Hormone Levels in Men with Coronary Artery Disease" has been submitted to Arteriosclerosis.

Professional Personnel Associated With the Research Effort

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Interactions

See List of Publications

New Discoveries

None

Other Statements

The studies performed in this investigation provide the first information ever obtained about the hormonal status of men with coronary artery disease before they have a myocardial infarction. This provides a unique insight into the role of hormones in the disease. Our finding that the elevated plasma estrogen levels we and six other research groups find in post-infarction patients are not present before the infarction sheds new light on this problem and forces a complete reassessment. We have developed testable hypotheses that are detailed above (Abstract).

# THE ROLE OF ENDOGENOUS HORMONAL FACTORS IN CORONARY DISEASE

Barnett Zumoff, M.D.

## Introduction

Coronary artery disease, in the form of its most important clinical manifestation, myocardial infarction, is a major cause of morbidity, mortality, and premature retirement in the armed forces. Epidemiological investigation has suggested that the classical, established risk factors for the disease, viz. hyperlipidemia, hypertension and cigarette smoking, account in the aggregate for only about one-half of its incidence in high-incidence populations such as that of the United States (1). Thus even if it were possible to decrease all of these factors simultaneously (as is attempted in the HEART studies in the Air Force and the MR FIT studies in civilian medicine), an excessive incidence of coronary artery disease would remain as a serious health problem. It appears essential, therefore, to develop new hypotheses to account for the remainder of this excess coronary artery disease incidence in order to devise appropriate methods for prevention and treatment.

## Epidemiological reasons for suspecting a relationship of hormonal factors to coronary artery disease

1. The fact that women show a strikingly lower death rate from coronary artery disease than men has been recognized for nearly 40 years (2,3). Since one might justifiably consider the essences of "maleness" and "femaleness" to be hormonal, this observation has focused interest on hormonal factors in coronary artery disease. Graphic representation (Fig. 1) of the relative death rates in men and women, adapted from the data of

Furman (4), shows the following points:

a. The rate is higher for men than for women at all ages, with the discrepancy most pronounced in the 30's, 40's and 50's, but declining somewhat at later ages.

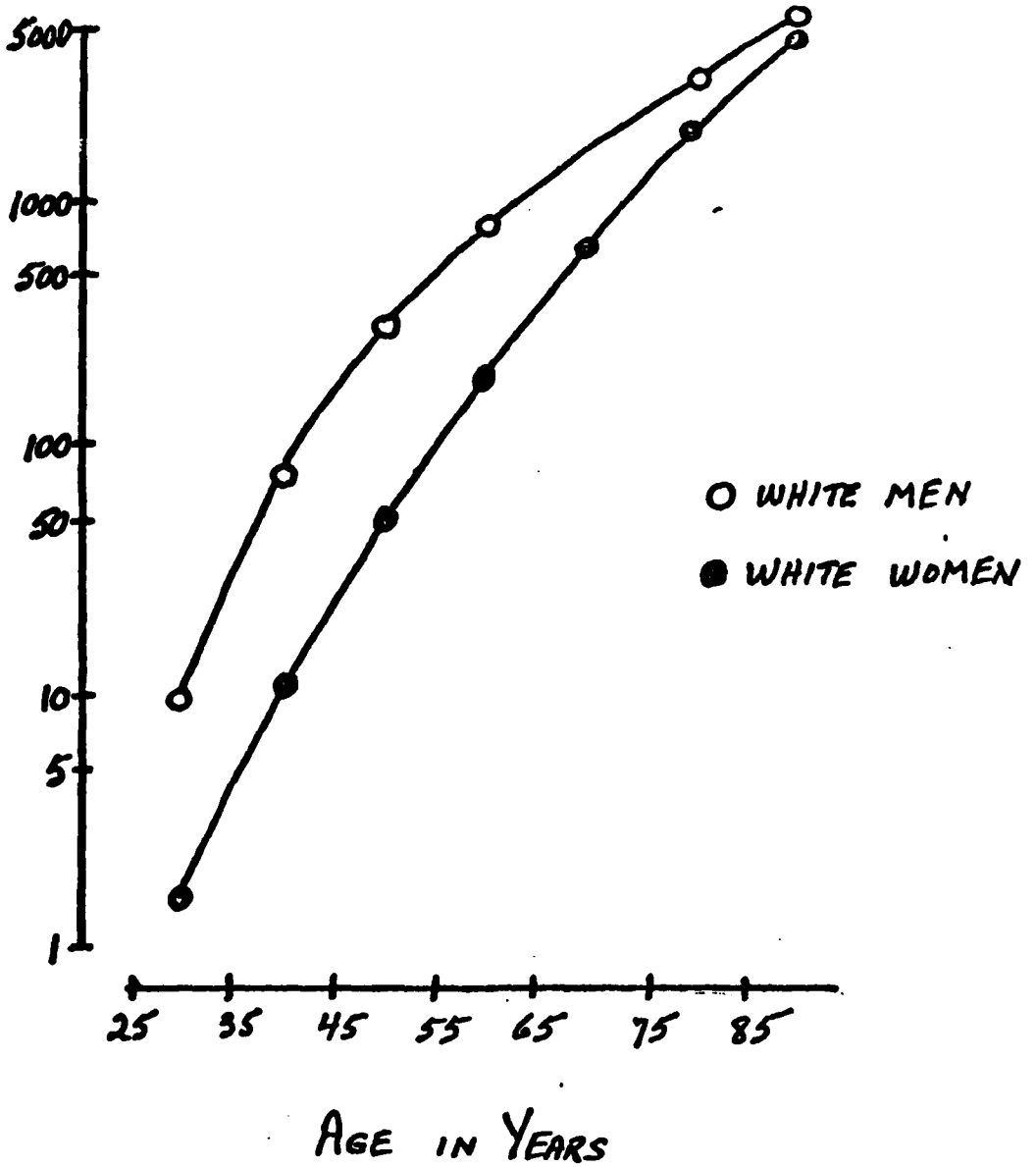
b. The rate increases with age in both sexes. The rate at which the rate increases gets smaller with age (i.e. the curve is concave downwards). This could mean one or more of three things: the factor(s) that cause the rate to rise with age become less prominent in older individuals; a highly susceptible young population dies off early leaving a less susceptible older population; protective factors appear increasingly with age.

c. Since the curves for men and women are qualitatively similar in shape, it is not possible to deduce from them whether the sex difference represents a protective effect of femaleness, a deleterious effect of maleness, or both. In this connection, it has been reported that ovariectomized women show increased coronary artery disease compared with intact women (5,6) and that orchiectomized men show decreased coronary heart disease compared with intact men (7); this suggests that the hormonal factors underlying the sex difference in coronary artery disease are probably bidirectional.

d. Since there is no upward discontinuity of the female curve at the menopause, there is no evidence that any protective effect of femaleness (if it exists) is necessarily related to physiological processes that diminish or cease at menopause (e.g. secretion of estradiol or progesterone). A direct test of the role of menopause was carried out a few years ago by the Framingham group (8): A group of women of

FIGURE 1

AGE-SPECIFIC DEATH RATE FOR CHD (DEATHS/100,000)



perimenopausal age was divided into 2 age-matched subgroups, one of women who were still menstruating and one of women who had ceased menstruating. It was found that the incidence of myocardial infarction was higher in the latter group. Unfortunately, the results may have been confounded by failure to stratify for cigarette smoking, which has been reported to cause earlier menopause (9-12) and which may therefore well have been more prevalent in the subgroup that had ceased menstruating.

Fig. 1

2. Premenopausal women who use hormonal contraceptives have more than four times as high an incidence of myocardial infarction as those who do not (13). At first glance, this observation that estrogen-progestagen combination therapy in women increases their susceptibility to coronary heart disease might appear to be in conflict with the epidemiologic evidence that women have coronary heart disease less frequently than do men. However, further consideration indicates just the opposite, namely that the contraceptive data strongly support the epidemiological conclusion that hormonal femaleness protects against coronary heart disease, for administration of hormonal contraceptives suppresses the secretion of endogenous gonadotropins and ovarian hormones and thereby deprives women of their normal, presumably protective, hormonal milieu. The synthetic estrogens and progestagens in the contraceptive pills may not possess the protective properties of their natural models, because of pharmacological differences, improper ratios of estrogen to progestagen, or abnormal relationships of the hormones to diurnal and/or monthly cycles, or because of a combination of these factors. This important point has great significance for the interpretation of the negative results of trials of "estrogen" prophylaxis against myocardial infarction.

3. Friedman and Rosenman and their colleagues (14) have described the association of a specific behavior pattern ("Type A") with a high incidence of coronary heart disease, and have suggested that the prevalence of this behavior pattern accounts for a substantial fraction of the excess incidence of coronary heart disease in the United States. A recent review (1) has brought together a large body of evidence confirming that this and related psychobehavioral factors do indeed affect

the incidence of coronary heart disease. It seems highly probable that the physical mediation of such effects of the psyche on the heart involves hormonal factors. Friedman's group suggested, as a first approximation, that the mediation might be via changes in catecholamine levels (15). They later reported (16) that there were subtle differences between "Type A" and "Type B" men in the pituitary-adrenocortical feedback relationship.

It should be emphasized that we are talking about the epidemiology of coronary artery disease and not about that of atherosclerosis. That these two entities are by no means equivalent is apparent from three facts: first, there can often be extensive aortic or cerebral-vessel atherosclerosis with little or no coronary artery disease, both in experimental animals and in humans (17); second, cerebrovascular accidents, which are largely due to atherosclerosis, have shown no increase in incidence over the past 60-year period (18) during which the incidence of coronary artery disease first increased 3-5 fold and more recently has fallen by about 25%; third, there is essentially no sex difference in the incidence of cerebrovascular accidents (19). The reasons for this disparate behavior between coronary artery disease and other manifestations of atherosclerosis are very obscure, but the findings strongly suggest that elevated lipids, atherosclerotic plaques, and thrombotic events (all of which are prominent in cerebrovascular disease) are not the whole story of the pathogenesis of coronary artery disease, and that the role of hormones in the sex differences may be in other areas, e.g. "myocardial factors" (19). It is worth noting, in this respect, that excess cortisol has been shown to have deleterious effects on the myocardium (20).

Abnormalities of steroid metabolism in diseases predisposing to coronary artery disease

Hellman and Fishman and their colleagues have described (21-24) profound changes in the metabolism of four secreted hormones (11-hydroxy-androstenedione, cortisol, estradiol, and testosterone) in hypothyroidism (Table 1).

Table 1

ABNORMALITIES OF STEROID METABOLISM IN HYPOTHYROIDISM

| STEROID STUDIED | METABOLITE(S) FORMED IN EXCESS | METABOLITES FORMED DEFICIENTLY |
|---|---|---|
| 11-hydroxyandro-stenedione | 3α,11β-dihydroxyandrost-4-en-17-one | 11-hydroxyandrosterone |
| cortisol | tetrahydrocortisol, cortol,β-cortol | tetrahydrocortisone, cortolone,β-cortolone |
| estradiol | estriol | 2-hydroxyestrone, 2-methoxyestrone |
| testosterone | etiocholanolone | androsterone |

Empirically, any or all of these changes might be involved in the predisposing tendency of hypothyroidism for coronary artery disease. That this possibility should be taken most seriously is suggested by the sequence of events concerning androsterone. Hellman et al reported in 1959 (24) that the formation of androsterone from androgen precursors was greatly diminished in hypothyroidism. Since it is well known that hypothyroidism results in elevation of the blood cholesterol level, these authors tested the possibility that administration of the deficient steroid (i.e. androsterone) might reverse this metabolic abnormality and lower the blood

cholesterol level. It was found (25) that injected androsterone did indeed rapidly and profoundly lower the elevated blood cholesterol level in hypothyroidism, and also lowered it when it was elevated from any other cause (familial hyperlipidemias, nephrosis, diabetes mellitus, etc.).

Previous empirical observations of hormonal abnormalities in coronary artery disease

1. Gertler and White, in 1956 (26), reported that young men with a history of prior myocardial infarction showed subnormal urinary 17-ketosteroid excretion.

2. Bauld et al, in 1957 (27), reported abnormalities of estrogen metabolism in such patients. They studied the urinary excretion of estradiol, estrone, and estriol, and found that these were normal under basal conditions but showed an abnormal response to short-term, moderate loading with estradiol: the excretion of estriol rose disproportionately to that of estrone and estradiol.

3. Bersohn and Oelofse, in 1958 (28), reported somewhat similar abnormalities in post-infarction patients: under basal conditions, excretion of estrone and estradiol was subnormal and there was an abnormally high ratio of estriol to these two.

4. Marmorston et al, in 1970 (29), reported that men with prior infarction showed subnormal urinary excretion of androsterone and elevated urinary excretion of the 11-oxy-17-ketosteroid metabolites of cortisol (viz. 11-hydroxyandrosterone, 11-hydroxyetiocholanolone, and 11-ketoetiocholanolone).

5. Rao, in 1970 (30), reported subnormal urinary androsterone excretion in men in the subacute post-infarction stage.

6. Wagner, in 1975 (31), found elevated plasma levels of ACTH, cortisol, growth hormone, testosterone, estradiol, and LH in a group of otherwise healthy men who had recovered from a myocardial infarction.

7. Troxler et al, in 1977 (32), showed that young men with coronary-arteriographically documented coronary artery disease but no history of myocardial infarction had greater secretion of cortisol in response to a standardized minimal stress (multiple venipunctures) than did age-matched men with arteriographically documented absence of coronary artery disease.

8. Phillips, in 1976 (33), reported elevated plasma levels of estrone and estradiol in young men (<40) who had recovered from a myocardial infarction. He reported a high incidence of clinical feminization (gynecomastia and decreased beard growth) in these men, a finding reported by no other investigator in this field.

9. Entrican et al, in 1978 (34), also described elevated plasma levels of estrone and estradiol in men who had recovered from a myocardial infarction.

10. Levin and Korenman, in an abstract published in 1978 (35), reported elevated plasma estradiol but not estrone in men in the subacute phase following an acute myocardial infarction.

11. Pivovarov et al, in 1978 (36), reported elevated plasma levels of ACTH, cortisol, growth hormone, testosterone, estradiol, thyroxine, and aldosterone in a group of men in whom coronary artery disease had been diagnosed by arteriogram, but in whom it is not clear how many, if any, had had a myocardial infarction. Estrone levels were not measured.

12. Pego et al, in an abstract published in 1979 (37), reported

elevated plasma estradiol levels in a group of men similar to those reported by Levin and Korenman. Estrone levels were not measured.

Relationship of hormonal factors to other factors that may affect sex differences in coronary artery disease

The data concerning sex differences in coronary artery disease that are discussed above relate to the white American population. In other populations, significant deviations from this pattern exist: among Japanese (in Japan), both sexes have a very low incidence and there is virtually no sex difference (38); the same is true among the Masai (39); among American Negroes, the sex difference seen in white Americans is nearly absent (40) because of a slightly lower incidence among males and a very greatly increased incidence among females. These differences between populations are sometimes used to support the conclusion that the sex difference in coronary artery disease is not "basic", and that hormonal factors underlying the sex difference are not of major importance in the natural history of the disease. Such a conclusion is illogical and unjustified, however. A more appropriate and almost self-evident conclusion is that hormonal factors can modify the clinical expression of other atherogenic factors only when the latter are operative to a significant extent in the population under study. It seems quite clear that coronary artery disease is of multifactorial origin and that changing any one of the factors concerned may have a profound effect prophylactically or therapeutically. There are at least four factors that interact in the production of myocardial infarction, the major clinical manifestation of coronary artery disease: the lipid composition of blood; the structure, nourishment, and composition of the arterial wall, which favor or resist

the development of atheromata; coagulation factors, which influence the development of thrombosis; and myocardial factors. There is an overwhelming body of experimental and epidemiological evidence that elevated blood lipids (precisely that constitutes elevation is not clear) are a necessary but not sufficient cause for the development of coronary artery disease. That is to say that in the absence of such elevation the disease will not develop to a significant extent, but that in its presence other factors come into play to determine the severity and extent of the disease. In this light, the low incidence among the Japanese and Masai is due to an absence of elevated blood lipids (among the Japanese, because of their protective diet; among the Masai, because of a probably genetic mechanism that protects them from their highly atherogenic diet [41]). The situation among American Negroes is probably different; here there may be countervailing deleterious factors among the females that nullify the protective hormonal effect. Some workers feel that the deleterious factor is hypertension, which is present in much higher incidence in Negro than in white women; others feel the deleterious factor may be a much higher incidence of Type A behavior among Negro than among white women, as a result of socioeconomic factors.

Comment concerning the results of trials of "estrogen" for the prophylaxis of myocardial infarction

Stimulated by reasoning similar to mine concerning the possible hormonal basis for sex differences in coronary artery disease incidence, a number of trials of estrogen for the prophylaxis of myocardial infarction have been carried out. The earliest of these were rather inconclusive;

some showed that estrogen protected against myocardial infarction (42,43) and some showed that it did not (43,44). The recent large-scale, well-controlled study by the Cooperative Drug Project (45,46) has appeared to show conclusively that estrogen does not protect against myocardial infarction. There are several reasons why these studies cannot be accepted as definitive proof that estrogen has no protective effect and certainly cannot be accepted as evidence that hormonal factors do not play a role in the sex difference in coronary artery disease incidence:

1. None of the trials used natural human endogenous estrogens. The pharmacological literature is replete with instances of subtle differences in effect between different synthetic hormones and their natural models. With respect to estrogens, for example, the synthetic compounds used in almost all contraceptives (viz. ethinyl estradiol and its 3-methyl ether, Mestranol$^{(R)}$) cannot be metabolized to 16α-hydroxy derivatives (i.e. analogues of estriol), but only to 2-hydroxy derivatives (47). The former remain estrogenic, while the latter are nonestrogenic and may even be antiestrogenic (48).

2. None of the trials was concerned with primary prevention -- all were secondary prevention trials.* Numerous authors have suggested on theoretical grounds that the latter offer the least possibility of demonstrating prophylactic effects; this view appears to be strengthened by the fact that there has been a favorable report on the prophylactic effect of clofibrate against myocardial infarction in a primary prevention trial (49) despite unfavorable reports in secondary prevention

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* Primary prevention is prevention of a first myocardial infarction in those who have never had one; secondary prevention is prevention of another infarction in whose who have already had one or more.

trials (45,46,50).

3. The assumption that femaleness equals estrogen effect is a gross oversimplification. Even at first glance, it is obvious that there are other hormonal sex differences, such as blood levels and production rates of testosterone and progesterone. A number of more subtle sex differences in hormone levels and metabolism have been observed and reported (Table 2), any or all of which might be responsible for a protective effect femaleness or a deleterious effect of maleness.

Table 2

SEX DIFFERENCES IN HORMONE LEVELS AND METABOLISM

| PARAMETER | DIRECTION OF DIFFERENCE | REFERENCE |
|---|---|---|
| Plasma testosterone | Men > Women | |
| " triiodothyronine | " | 51 |
| Urinary androsterone/etiocholanolone ratio after a testosterone tracer | " | 52 |
| Plasma estradiol | Women > Men | |
| " estrone (luteal) | " | |
| " progesterone (luteal) | " | |
| " dehydroisoandrosterone and DHA/DHAS ratio | " | 53 |
| Urinary excretion of nonglucuronide metabolites of an estradiol tracer | " | 54 |
| Urinary excretion of nonglucuronide metabolites of a tracer of dehydroisoandrosterone sulfate | " | 53 |
| Urinary excretion of androsterone and etiocholanolone after a DHAS tracer | " | 53 |
| 17-Oxidation of an estradiol tracer | " | 55 |
| 2-Oxidation of an estradiol tracer | " | 55 |

4. It is not at all clear that the sex difference in coronary artery disease is due only to protection by femaleness, as opposed to increased susceptibility because of maleness. As mentioned earlier, available data suggest that the sex difference is most likely bidirectional. Thus tests of ways to decrease blood androgen levels or antagonize androgen effects are just as important as tests of ways to increase femaleness.

Selection of patients for future studies of hormonal levels in coronary artery disease

The design of studies of hormone levels in coronary artery disease is exceedingly simple in principle: one merely compares the levels of men who have coronary artery disease with those of men who do not. However, determination of who does and who does not have coronary artery disease is not so simple in practice. Absolute certainty requires that the coronary arteries be examined at autopsy, and it would be difficult to study a patient's hormone levels after he had been autopsied. What has been done in all the studies described earlier in this essay is to use "clinical normals" (i.e. men with a normal history, physical examination, and electrocardiogram) to represent men without coronary artery disease, and men who have had one or more myocardial infarctions to represent men with coronary artery disease. This experimental design has certain weaknesses: first, the group of "clinical normals" contains some men with occult coronary artery disease, though this is probably a fairly small source of error in carefully screened groups; more important, I think, is that a patient who has suffered a myocardial infarct has undergone a complex physiological, psychological, and metabolic catastrophe

from which he probably never re-emerges the same person he was before the acute episode. The abnormalities observed in post-infarct patients may well be only a consequence of the infarction. In the optimal design of hormonal studies, therefore, it is desirable, indeed essential, to study patients with proved coronary artery disease who have never had a myocardial infarction. Such patients must be defined by the presence of a conclusive diagnostic criterion for coronary artery disease. Only one such criterion exists in the living patient: arteriographically-demonstrated coronary artery stenosis. Ideally, then, a comparison of men with coronary disease against men without coronary artery disease should be a comparison of men with positive coronary arteriograms against men with negative coronary arteriograms. No comprehensive study with such a design has been published, though Troxler et al (32) reported plasma cortisol levels in these two groups. Future studies should compare the hormonal status of arteriogram-positive and arteriogram-negative men, and contrast the results of this comparison to those of a comparison of "clinical normals" and post-infarction patients; this would distinguish the abnormalities that are associated with coronary artery disease *per se* from those that are observed only after a myocardial infarction.

Summary

The epidemiological reasons for suspecting a relationship of hormonal factors to coronary artery disease are discussed and the findings of various investigators concerning plasma and urinary hormone levels in men with the disease are reviewed. It is pointed out that future studies should investigate men with arteriographically-proved coronary artery stenosis who have not had a myocardial infarction, in order to distinguish the abnormalities that are due to coronary artery disease *per se* from those

that are consequences of an infarction.

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Comprehensive list of research objectives

The objectives of this study were:

(1) to compare the 24-hour mean plasma concentrations of 14 hormones or hormone metabolites in clinically normal men and men who have had one or more myocardial infarctions

(2) to compare the same parameters in men with negative coronary arteriograms and men with positive arteriograms but no history or evidence of myocardial infarction

(3) to compare the urinary excretion of 15 hormones or hormone metabolites in men with positive and negative arteriograms.

The purpose of these studies was to determine whether hormonal abnormalities were present in coronary artery disease, with or without myocardial infarction, and to distinguish abnormalities associated with coronary artery disease per se from those that appear only after myocardial infarction.

Status of the research

The studies have been completed. A manuscript describing the results (attached) has been submitted to Arteriosclerosis.

List of Publications

1. I gave a presentation on April 21, 1979 at Ramapo College of New Jersey, in Mahway, N.J., as part of a symposium entitled "The Sciences at the Forefront of Cardiovascular Research". The title of my presentation was "Plasma Hormone Concentrations in Coronary Disease." The proceedings of this conference will be published in 1981.

2. I gave a presentation on June 3, 1980, at Searles Castle, Great Barrington, Massachusetts, as part of a symposium sponsored by the NHLBI on the topic "The Influence of Female Sex Hormones on Vascular Disease and Thrombosis." The title of my presentation was "Plasma and Urinary Hormone Levels in Men with Coronary Artery Disease." The proceedings of this conference will be published in 1981.

3. In 1980, I submitted an essay entitled "Plasma and Urinary Hormone Levels in Men with Coronary Artery Disease" for the annual AMSUS competition for the Sir Henry Wellcome Medal. I was not selected for the prize but a portion of the manuscript is to be published in Military Medicine in 1981 (manuscript attached).

4. A manuscript (attached) entitled "Plasma and Urinary Hormone Levels in Men with Coronary Artery Disease" has been submitted to Arteriosclerosis.

Professional Personnel Associated With the Research Effort

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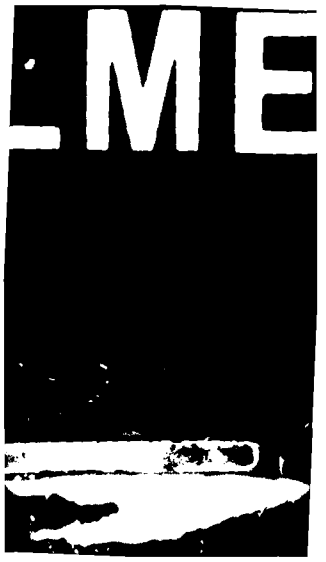
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